

## SOUTHWEST ONCOLOGY GROUP

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### PROTOCOL GUIDELINES

#### **A. GENERAL INFORMATION FOR PROTOCOL FORMAT, DEVELOPMENT AND ADMINISTRATION**

By reviewing these guidelines, a protocol author helps to ensure prompt and efficient processing of the study.

1. To be a Study Coordinator, an individual must be a member of the Southwest Oncology Group and must have completed the Group's online Study Coordinators' Workshop.
2. Each section title of the protocol should be capitalized and the sections must appear in the order listed below. Standard sections to be included in all protocols are:

- SCHEMA
- 1.0 OBJECTIVES
- 2.0 BACKGROUND
- 3.0 DRUG INFORMATION
- 4.0 STAGING CRITERIA
- 5.0 ELIGIBILITY CRITERIA
- 6.0 STRATIFICATION FACTORS
- 7.0 TREATMENT PLAN
- 8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS
- 9.0 STUDY CALENDAR
- 10.0 CRITERIA FOR EVALUATION
- 11.0 STATISTICAL CONSIDERATIONS
- 12.0 DISCIPLINE REVIEW
- 13.0 REGISTRATION GUIDELINES
- 14.0 DATA SUBMISSION SCHEDULE
- 15.0 SPECIAL INSTRUCTIONS
- 16.0 ETHICAL AND REGULATORY CONSIDERATIONS
- 17.0 BIBLIOGRAPHY
- 18.0 MASTER FORMS SET
- 19.0 APPENDIX

The contents of each section are defined in Section G.

3. Protocol Development and Administration

The goal of centralized protocol development in the Southwest Oncology Group is to speed development and standardize quality and format of the most important studies in the judgment of the Committee Chair within every disease committee of the Group. This process includes central review of all studies by the Group administration at the earliest possible time in the development process. These recommendations follow the order of events outlined on the protocol development schema (page 6 of policy). Protocol status reports will be maintained on the Group web site and development time will be tracked for the top priority protocols per Committee (page 7 of policy), and provided to the respective Study Coordinators and Committee Chair at least semi-annually, and more often upon request. The Group's Executive Committee will review development time for the top priority studies on a quarterly basis (or more often as particular situations warrant) and will recommend a corrective action plan involving action by the Protocol Coordinator, the Study Coordinator and/or the Committee – as needed – for any study where the Executive Committee identifies that intervention is needed. If corrective action is not taken within the timeframe specified in the corrective action plan, the protocol may be removed from its priority slot and/or tabled.

Other studies in development within the Committee will also be ranked. Protocol development for lower priority studies will continue to be monitored, and will be actively pursued by the Protocol Coordinators as time and competing priorities allow.

### **PERSONNEL INVOLVED IN PROTOCOL DEVELOPMENT**

#### **Protocol Coordinator/Operations Office**

The protocol development responsibilities of a Protocol Coordinator for the Southwest Oncology Group are:

- To coordinate and assist in the development and activation of studies to be performed within the Southwest Oncology Group and to ensure that this is done in a timely fashion.
- To assist the Study Coordinators by sending them information, answering questions and providing clarification regarding the protocol development process and Group procedures.
- Specifically, to coordinate the development of each proposed study through activation including:
  - putting proposed studies into a proper and acceptable format, and
  - making sure that all pertinent physician coordinators, Statisticians and Committee Chair perform a detailed review of the study and incorporate comments and changes into the study.
- To serve as a liaison between the National Cancer Institute (NCI) and the Committee.
- To ensure that the study is consistent in content and contains all the information that is required by the NCI and the Group.
- To submit the study to the NCI for review and distribute information about the study (such as approval or disapproval) to the appropriate individuals.

#### **Director of Operations and Protocols/Operations Office**

The Director of Operations and Protocols is responsible for assisting the responsible Protocol Coordinator in the prompt development of the top priority protocols per Committee, and providing overall leadership, training and consistency across Committees in protocol development and maintenance.

#### **Study Coordinator**

The Study Coordinator is the primary advocate for an idea within the Group. The Study Coordinator is the Group member who proposes a study, is the primary force in developing the capsule summary into an activated protocol in a timely fashion, is responsible for answering questions regarding medical and scientific issues that arise during the conduct of the study, expeditiously responding to requests from the Statistical Center and analyzing the data in conjunction with the Committee Statistician, and writing the manuscript summarizing the results of the trial. Investigators in the Southwest Oncology Group who coordinate a Group trial must adhere to the requirements listed herein. In addition, the investigator must complete the Group's Study Coordinator Workshop prior to receiving approval to coordinate a Southwest Oncology Group trial. This workshop provides a detailed overview of each responsibility (Protocol Development, Study Monitoring, Study Evaluation, Reporting of Results, etc.). Except in unusual circumstances, a Study Coordinator may not be primary coordinator of more than one Southwest Oncology Group-coordinated Phase III clinical trial at a time.

By Group definition, coordinating a clinical trial means involvement from the capsule summary stage to the submission of a manuscript. Study Coordinators are required to submit a disclosure of any significant financial conflict of interest that they may have in conformity and compliance with the Group's Conflict of Interest Policy #35.

### Executive Officers

The protocol development responsibilities of the Executive Officers are:

- To continually assess the committee priorities in relation to Group priorities.
- To evaluate each study proposal's merit in terms of its fit with the Group mission.
- To provide leadership consistency across committees.
- To participate in protocol review.
- To assist in the review of protocol development timelines.

## **PROTOCOL DEVELOPMENT PROCESS**

### **CAPSULE SUMMARY PHASE**

The Study Coordinator is initially responsible for proposing a new idea to the Committee and the Group. The Study Coordinator must receive approval from the Committee Chair of the responsible committee to proceed with development of a capsule summary. When a new protocol (or an amendment to an existing protocol) is identified where the eligibility crosses traditional committee boundaries, the Protocol Coordinator will take the following steps:

- 1) contact the chair of the proposing committee to find out whether the chair of the "secondary" committee has agreed that this protocol, committee assignment and inclusion criteria are appropriate
- 2) contact the chair of the "secondary" committee to assign a secondary Study Coordinator from their committee
- 3) ensure that both the "secondary" committee chair and assigned Study Coordinator are copied on circulation of all formal protocol drafts - to ensure opportunity for comments
- 4) enter the involvement of the additional committee into the publication tracking system to insure that each committee is recognized for its input.

The Protocol Coordinator will serve as a resource for information and distribution of information during this phase. The Protocol Coordinator will assist in preparing a capsule summary from information provided by the Study Coordinator (pages 8-9 of policy). The Protocol Coordinator provides the capsule summary to the Director of Operations and Protocols for placement on the agenda for the Executive Conference, comprised of leadership from the Group Chair's Office, Operations Office and Statistical Center. Approval of the capsule summary will depend on feasibility and priority within the Group, and current workload in the Operations Office and Statistical Center.

Following review by the Executive Conference, the decision and specific comments will be communicated to the Study Coordinator and Committee Chair with a copy to the Protocol Coordinator, and to other individuals involved in the review process, for official record-keeping.

Upon receiving the Committee Chair's priority ranking, the Protocol Coordinator will contact the Study Coordinator and the Committee Biostatistician with specific information on the study's priority ranking and its significance. The Protocol Coordinator will provide the Study Coordinator with information about proceeding with the Concept Blueprint Phase. Studies may be re-prioritized at the discretion of the Committee Chair.

The Committee Chairs will be asked to re-prioritize the studies within development in their Committee whenever a new capsule summary is approved.

### **CONCEPT BLUEPRINT PHASE**

In this phase, the capsule summary is expanded to provide information for a formal Letter of Intent (LOI) or concept submission. Upon entry of a study into the Protocol Blueprint Phase, the Protocol Coordinator will then assist the Study Coordinator in finalizing the requirements of the scientific portion of the Concept Blueprint and will begin working with the Director of Operations

and Protocols toward fulfilling the requirements of the administrative section. Budget development and contract negotiations will take place simultaneously with finalizing the scientific portions of the blueprint. The Study Coordinator and Committee Chair will be kept apprised of progress and problems and/or delays in completing the administrative section.

#### Scientific Section

The scientific section of Phase III trials will involve detailed description and justification for selection of the control and experimental arms. The control arm should be selected so that it conforms to best standard therapy that has been defined in previous clinical trials and/or represents standard of care in the community. Selection of the drugs, doses and schedules for the experimental treatment arm should be based on the results of Phase II (or in rare instances, completed Phase I) clinical trials. Modification of the drugs, doses, or schedules from the Phase II experience is to be discouraged. The Study Coordinator should then contact the Committee Statistician to discuss determination of primary and secondary endpoints, ancillary study endpoints, and sample size for the trial.

In the case that ancillary studies are to be done, it is the Study Coordinator's responsibility to identify sources of funding to accomplish those ancillary studies and to notify the Director of Operations and Protocols and the Protocol Coordinator of the contact personnel with whom contract negotiations or grant submission can be initiated. Potential funding sources include R-O1 or R-O3 grants from the National Cancer Institute, supplemental funding to the Southwest Oncology Group U-O1 grant, institutional grants, and a pharmaceutical sponsor, to name but a few. It is imperative that funding sources be obtained prior to the initiation of the development of the protocol document.

In conjunction with discussions with the Committee Statistician, Executive Officer and the Committee Chair, the Study Coordinator must assure that the eligibility criteria for the study are written in such a way that there will be adequate patient availability to complete the planned accrual in an appropriate period of time. If any significant differences of opinion develop, they should be discussed among all participants through a conference call. The final eligibility criteria for the study are then developed with input from other modality chairs (e.g., surgical oncology, radiation oncology), where appropriate.

The Executive Officer is expected to contact the CTEP drug monitor and/or the CTEP disease liaison for informal feedback as needed. The information provided to the CTEP liaison should be sufficient to determine whether this study overlaps or is duplicative of another trial previously approved by CTEP, potential conflict of this study with another previously approved or ongoing study, availability of the investigational drug (if one is involved), and any advice or suggestions that the CTEP staff member may have regarding the overall concept that is being proposed.

In trials involving multimodality therapy as part of the therapeutic protocol, input from all involved modalities must occur throughout the capsule summary, concept blueprint and protocol development phases. Modality input during the concept blueprint phase refers to defining modality-specific criteria for inclusion in the concept.

The process for development of a Phase II trial proceeds along a somewhat similar pathway. Selection of the drug, dose and schedule should be based on the results of Phase I or preliminary Phase II data. From that point on, the elements in protocol development are similar up to the point of preparation of an LOI for submission to CTEP by the Protocol Coordinator and Operations Office.

#### Administrative Section

Some studies may involve investigational new drugs (INDs) obtained directly from a pharmaceutical company, or ancillary or other studies that require additional financial support. Such protocols require additional administrative support from the Operations Office. Should the study involve an investigational new drug obtained directly from a pharmaceutical company, the

Study Coordinator should provide the Operations Office with the name of a contact person at the company who will be able to negotiate a contract for support of this study within the Southwest Oncology Group.

It will be the responsibility of the Operations Office staff to ensure adequate drug supply for the study, to arrange drug distribution, to address regulatory issues such as IND filing, to determine the extent of data above and beyond Group norms that will be required for this study, and to develop a budget and contract that will cover the costs for these elements in the conduct of the study. The Operations Office staff will be responsible for keeping the Study Coordinator and the Committee Chair apprised of the status of these negotiations.

In the event of ancillary or other studies, it will be the responsibility of the Study Coordinator to identify sources of financial support for these studies. The Operations Office staff will be available to assist with this process.

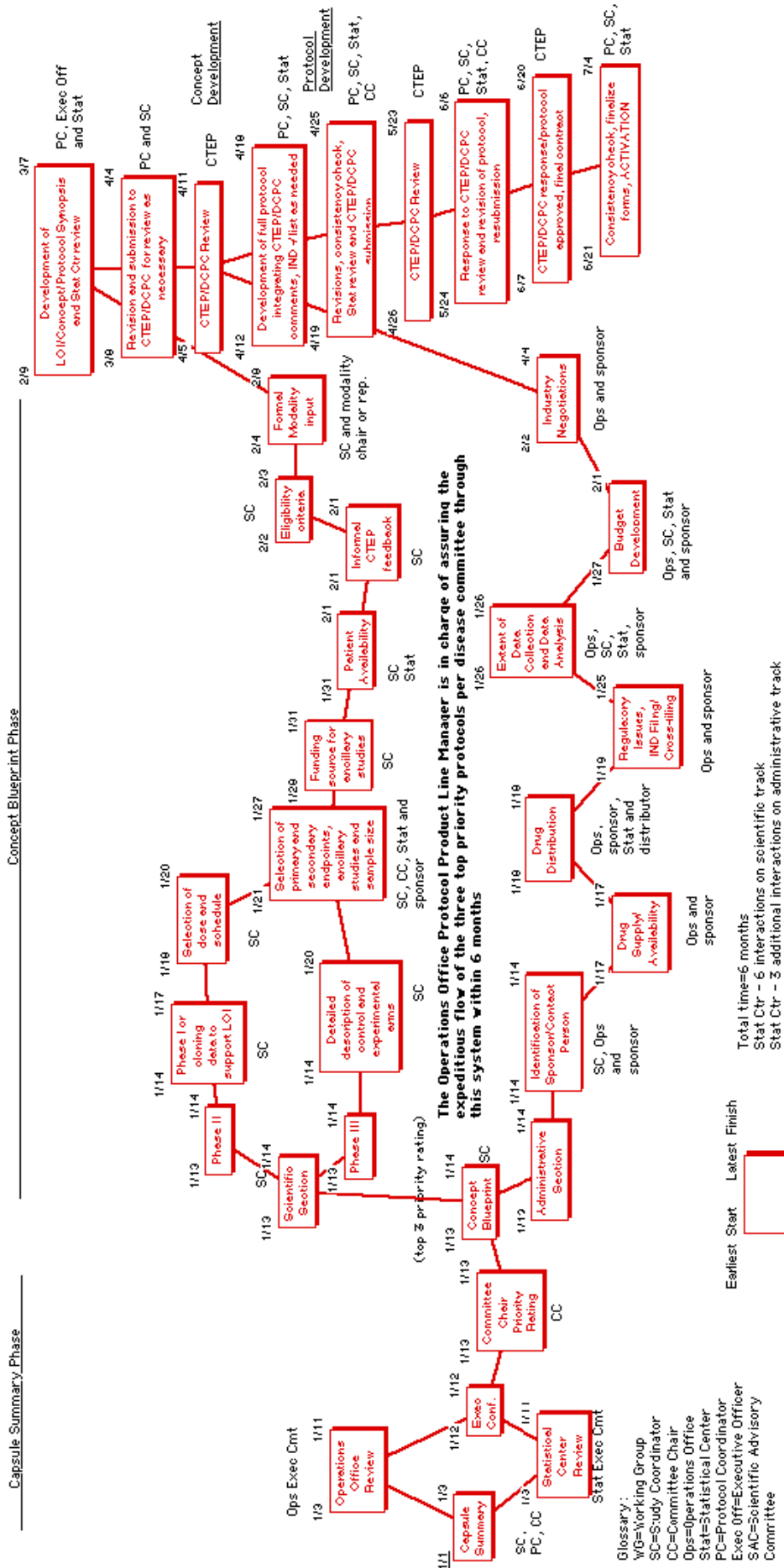
### **CONCEPT DEVELOPMENT**

Once all elements of the blueprint have been completed, the Protocol Coordinator is then responsible for development of an LOI (if it is a Phase II trial involving an investigational drug supplied by the NCI, see [http://ctep.cancer.gov/protocolDevelopment/docs/loi\\_form.doc](http://ctep.cancer.gov/protocolDevelopment/docs/loi_form.doc)) or concept (if it involves a comparative Phase III trial, see [http://ctep.cancer.gov/protocolDevelopment/docs/Concept\\_Submission.doc](http://ctep.cancer.gov/protocolDevelopment/docs/Concept_Submission.doc)) which is reviewed by the Executive Officer, the Study Coordinator, the Committee Chair, the Committee Statistician and the Statistical Center review committee for accuracy and completeness. Note: The scientific rationale for the study must be sufficiently supported in the concept/LOI document. The concept/LOI is then submitted to CTEP for review. If substantial changes are suggested or mandated by CTEP, the concept/LOI may need to start over from the Capsule Summary phase. A traditional intergroup study should have formal commitment from the other participating group(s) before proceeding with submission of the concept.

### **PROTOCOL DEVELOPMENT**

If the concept is approved by the NCI with no significant changes to elements of the blueprint, protocol development may now proceed. The Protocol Coordinator now becomes the pivotal person in the development process. All important elements of the study should be in place to develop the concept into a full protocol. The Protocol Coordinator will be responsible for completing the remaining steps in development and activation in a timely fashion. CTEP's comments regarding the concept or LOI will be forwarded to the Study Coordinator, Committee Chair, Committee Statistician, and Executive Officer for review. The Study Coordinator and Committee Statistician in conjunction with the Protocol Coordinator will be responsible for integrating those revisions into the full protocol. Once the full protocol has been developed, it will be circulated among the Study Coordinator, Committee Statistician, Committee Chair and Executive Officer for revisions, consistency check, and statistical and data coordination review prior to submission of a full protocol to CTEP. Upon receipt of CTEP's review of the protocol, those comments will be circulated to the Study Coordinator, Protocol Coordinator, Committee Statistician, Committee Chair, and Executive Officer for review. The Study Coordinator and the Committee Statistician will be responsible for responding to all of CTEP's comments and the Protocol Coordinator will be responsible for generation of a revised protocol. The revised protocol will once again be circulated to the Study Coordinator, Committee Statistician, Committee Chair, and the Executive Officer for review and comment prior to submission to CTEP. Barring any additional comments or concerns by CTEP, the protocol will be activated within the Southwest Oncology Group upon final approval from CTEP or DCP.

Title, date of top 2 or 3 priority  
**Protocol Development**



**PRIORITY SLOTS**

Committees	Priority slots
Breast	3
Cancer Survivorship	3
Gastrointestinal	3
Genitourinary	6
Gynecologic	2
Health Disparities and Outcomes	3
Leukemia	3
Lung	3
Lymphoma	3
Melanoma	2
Molecular Epidemiology	3
Myeloma	2
Prevention	3
Symptom Control and Quality of Life	3
Translational Medicine	2

**CAPSULE SUMMARY**

Disease Committee and Site: \_\_\_\_\_

Number of approved studies already in development in this committee: \_\_\_\_\_

Active competing studies in the committee (with current accrual and planned closure date): \_\_\_\_\_

Proposed competing studies in development: \_\_\_\_\_

Committee plan for competing studies: \_\_\_\_\_

Approximate priority in the committee if approved: \_\_\_\_\_

Does this protocol involve surgery and/or surgical evaluation?  Yes  No

Does this protocol involve surgical staging after protocol registration?  Yes  No

Does this protocol involve surgeon's evaluation of resectability?  Yes  No

If YES to any of these, identify the surgeon who reviewed the protocol: Surgeon: \_\_\_\_\_

What is the category of surgical review?  I  II  III (please refer to the description of the Surgical Quality Assurance Program as needed)

If category II or III, who is the Surgical quality assurance reviewer: \_\_\_\_\_

Committee Chair and approval date: \_\_\_\_\_

Intergroup: Yes/No (circle one)      Coordinating group: \_\_\_\_\_

*If coordinated by another group, active:* Yes/No (circle one)      Current accrual: \_\_\_\_\_

Study Coordinator: \_\_\_\_\_ SCWS date: \_\_\_\_\_

Study Coordinator's institution: \_\_\_\_\_

Previous or current Young Investigator Training Course attendance? Y / N

Title: \_\_\_\_\_

Primary study objective: \_\_\_\_\_

Brief justification (background and rationale – include top 3-5 references): \_\_\_\_\_

Eligibility: \_\_\_\_\_

Treatment: \_\_\_\_\_

Endpoint(s): \_\_\_\_\_

Other Statistical Considerations: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Estimate of Sample Size: \_\_\_\_\_

Estimate of Accrual Rate: \_\_\_\_\_

**Special Considerations:**

1. Will there be drug company support for the study (YES/NO)? \_\_\_\_\_

Name of drug company: \_\_\_\_\_

If so, will the company be supplying drug/distribution (YES/NO)? \_\_\_\_\_

What is the distribution mechanism? \_\_\_\_\_

Will an IND be required (YES/NO)? \_\_\_\_\_

Will the drug company offer additional monetary support (for correlates, data management, or per case payments) (YES/NO)? \_\_\_\_\_

If yes, explain: \_\_\_\_\_

Contact person at drug company, if available:

Name (and title):

Address:

Phone:

Fax:

Email:

2. Are there correlative studies planned (YES/NO)? \_\_\_\_\_

If so, what funding is available for correlative studies or how will funding be sought? \_\_\_\_\_

3. Anticipated CTEP Submission Date \_\_\_\_\_

Other Additional Comments: \_\_\_\_\_

\_\_\_\_\_

## POST-ACTIVATION

During the course of the study, occasions may arise to change parts of the study. The following is a list of protocol actions and their definitions.

- a. Amendment: A change to the protocol that directly affects patient care or treatment and may substantively increase the patient's risk/benefit ratio.
- b. Revision: An administrative or editorial change that does not affect patient care or treatment, or a scientific or medical change that does not substantively increase the patient's risk/benefit ratio.
- c. Memorandum: Explanation of a study concept or other information about the study that do not change the study itself.
- d. Temporary Closure: Initial accrual on a Phase II study has been met, or death or severe toxicity that may be related to treatment has been reported, or other logistical reason for closure.
- e. Permanent Closure: The accrual goal has been met for the study, or the required tumor response has not been seen to reopen a study that was temporarily closed, or a decision has been made that the accrual goal for the study is not likely to be met.

**TO ALLOW ADEQUATE NOTICE, NOTIFICATIONS REGARDING ROUTINE CLOSURES ARE POST-DATED BY TWO WEEKS (I.E., A NOTICE WILL BE DISTRIBUTED ON SEPTEMBER 1 NOTIFYING THAT THE CLOSURE WILL BE EFFECTIVE SEPTEMBER 15). EMAIL DISTRIBUTIONS OF CLOSURE NOTICES WILL BE ROUTINELY SENT TO THE PRINCIPAL INVESTIGATORS OF ALL GROUP INSTITUTIONS TO ALLOW MORE TIME FOR PROCESSING.**

Priority Lists are committee specific lists of all open and temporarily closed protocols within that committee. Disease sites are grouped together and studies are placed in the order of their priority for patient entry. Institutions will not routinely be able to participate on competing studies for the same type of tumor. The list is distributed via the web site and shows which institutions can enter patients on each study. Priority lists are updated only when there has been a change such as activation of new study, a temporary or permanent closure, or change in participants.

### **B. PHASE I STUDIES**

Administratively and functionally, a Phase I trial in the Southwest Oncology Group is defined as a trial in which the assessment of safety and documentation of adverse effects is of primary importance. Some Phase I trials may be done to establish a dose (e.g., MTD) and/or schedule of an agent or agents. A secondary interest is to ascertain whether there is preliminary evidence for antitumor effect.

Generally, a Phase I trial conducted in the Group will be one of three types: 1) Phase I studies for which the NCI holds the IND (Investigational New Drug), 2) Phase I studies for which the Southwest Oncology Group holds the IND, and 3) Phase I studies for which IND drugs are not involved. The expectations of the involved parties and the procedures used to conduct the trial will vary according to the type of Phase I trial being conducted.

Phase I studies will be developed within the Early Therapeutics Subcommittee of the Translational Medicine Committee.

### **C. PHASE II STUDIES**

Phase II investigational drug studies may involve the creation of a new drug information section and consent form toxicity section. The creation of these sections is the responsibility of the Pharmaceutical Sciences Committee and the Operations Office. Otherwise, the Study Coordinator is responsible for developing the protocol in its entirety, but may use other protocols for guidance. Other Phase II studies may include studies of single commercially available agents or a combination of investigational and

commercial agents. Phase II studies may also include studies of surgery or radiotherapy alone or in conjunction with chemotherapy. These protocols are developed in the same manner as other studies.

#### **D. PILOT STUDIES**

For studies using no investigational drugs provided by the NCI and fewer than 100 patients, the NCI review is limited to "developmental strategy" (review at this stage provides the Group with an early indication of the potential scientific value of an eventual Phase III question). There is no limit to the number of institutions that may participate. Pilot studies (which may or may not use investigational agents) are performed to supply data for future Phase III studies. Pilot studies for Group Phase III studies should be performed within the Group. (See Policy Memorandum #28 for details.)

#### **E. CANCER CONTROL AND ANCILLARY STUDIES**

Development of Cancer Control studies is similar to the development of treatment protocols – except that the concept is submitted to the NCI's Division of Cancer Prevention (DCP). Upon DCP's concept approval, the Study Coordinator(s) develop the protocol which is submitted to the NCI. Usually, DCP's consensus review requires that the study be revised in specific ways. Revisions are made and the study is returned to DCP for a second review. Following DCP's approval of the study, the protocol is activated.

Ancillary studies are developed like treatment protocols within the disease committee.

#### **F. PHASE III STUDIES**

Phase III studies are designed to establish the usefulness or value of a new treatment. This may be accomplished through a number of study designs. For instance, a standard treatment can be compared to a standard treatment plus a new agent. A previously accepted standard may be compared to an equally toxic or potentially less toxic new agent. Other possibilities of comparisons include new drugs being combined with a previously accepted combination of active drugs or combining types of treatment such as chemotherapy followed by surgery versus surgery alone. In some cases Phase III studies may contain several arms. A comparison of a new regimen to several standard treatments is one example of this.

Study requirements for a Phase III trial are that: 1) the patient has a certain tumor type; 2) the patient usually has received no prior treatment; and 3) a large number of patients must be entered onto the study in order to demonstrate a difference between types. Phase III studies usually take 3-5 years to complete.

Phase III study results show whether the new type of treatment is better than the standard therapy in regard to tumor type, toxicities experienced, improved survival and quality of life.

#### **G. PROTOCOL GUIDELINES**

##### **SCHEMA**

Schemas are included only for complicated Phase II protocols and all Phase III protocols. The Operations Office will prepare a final schema to be attached to the protocol when it is submitted for NCI review. Given the possibility that investigators may attempt to treat patients using the information provided in the schema without referring to the treatment plan details, any specific treatment details, i.e., treatment dose(s), schedule, must not be included in the schema.

##### **1.0 OBJECTIVES**

- 1.1 The objectives should pose important scientific questions to be answered by the study. These include the value of a new investigational drug or a new combination of treatments, or a comparison between standard therapy and innovative new treatment. The objectives should be obtainable with the sample size of the study. Phase II example: "To assess tumor response to esorubicin in patients with advanced breast cancer and one prior chemotherapeutic regimen for advanced disease." Phase III example: "To compare cyclophosphamide plus 5-fluorouracil plus tamoxifen to tamoxifen alone with respect to survival and time to progression in postmenopausal breast cancer patients with recurrent disease."

- 1.2 Do not abbreviate the drugs to be used, and list them by generic name (cyclophosphamide vs. Cytosan).
- 1.3 State the endpoints of interest (response, disease-free survival, time to progression, survival, etc.).

## **2.0 BACKGROUND**

The background justifies the objectives by summarizing the results of similar studies. Include the therapeutic effectiveness of the proposed regimen, if known. Information obtained in animal studies or in pilot studies performed in humans will suffice. Background information is required on all modes of treatment which will be used.

For those studies evaluating a totally new treatment regimen (such as an investigational drug at a new dose or schedule), pilot data, with favorable results, are required to justify using the new therapy on a group-wide basis.

There should be no abbreviated words within the background section and this section should be written in complete sentences. The Southwest Oncology Group should be spelled out ("SWOG" is used for numbering purposes only). Paragraphs are not numbered. All references should be numbered in the order they appear in the text and included in the bibliography.

The background for a Phase II protocol should be limited to one page (front and back) in length. The background for a Phase III protocol should be limited to one and one-half pages (front and back).

## **3.0 DRUG INFORMATION**

The Operations Office will provide the entire drug information section for those drugs which are available commercially, or for those investigational drugs which have been previously used in protocols. The author may put "information supplied by the Operations Office" and the information will be inserted when the final draft is being prepared for NCI review. For the drugs not previously used in a protocol, as mentioned above, the Study Coordinator must contact the Operations Office to begin the process for developing a drug information section through the Pharmacy Committee.

- 3.1 All drugs being utilized in the proposed study should be described. Standard sections required by the NCI are: Human Toxicity, Pharmaceutical Data, Administration, Storage & Stability, and Supplier.
- 3.2 The drugs should be listed in alphabetical order.
- 3.3 The National Service Center (NSC) number should be given along with other standard names for the drug. If the drug is investigational, the Investigational New Drug (IND) number should also be supplied.
- 3.4 The supplier should be correctly given. Many of the drugs standardly obtained from the NCI in the past are now available by commercial means only.

## **4.0 STAGING CRITERIA**

The criteria by which patients should be staged should be provided, or state if staging is not applicable. Reference standard criteria instead of reproducing them, when appropriate. Define only those stages needed to determine eligibility.

## 5.0 ELIGIBILITY CRITERIA

For Phase II studies, there may be standard eligibility criteria derived from the committee's history of prior studies. For Phase III studies, eligibility criteria will be supplied by the investigator. Certain requirements are standard (e.g., performance status, prior malignancies, time constraints for performance of prestudy tests) and are added by the Operations Office. In order to prevent impediments to clinical trial participation from arising and to help increase accrual to clinical trials, Study Coordinators are asked to simplify eligibility criteria by following these guidelines:

- 5.1 There should be a sound scientific basis for every eligibility requirement listed in Section 5.0 of the protocol. If any of the requirements is not likely to have a significant impact on issues of patient safety or data interpretation, strong consideration should be given to leaving that criterion out of Section 5.0.
- 5.2 Every effort should be made to limit the requirements for studies or procedures performed prior to registration since many of these procedures are performed by non-Group members (e.g., staging and debulking laparotomy for women with advanced stage ovarian cancer, minimum number of lymph nodes that are required for women with localized or locally advanced breast cancer, number of lymph nodes sampled in patients resected for head and neck cancers, etc.). Inclusion of such requirements should be based on evidence that non-adherence to these standards will have a substantial impact on the course of disease, response to therapy, or interpretation of the data.
- 5.3 Careful consideration should be given as to whether central pathology review should be required for the study. In diseases for which there is general agreement between pathologists regarding essential aspects of diagnosis (tumor grade, histologic subtype, etc.), central pathology review may not be necessary.
- 5.4 The current time frames required for prestudy tests appear to be reasonable and strike a good balance between the avoidance of repeating tests that would not be medically warranted and obtaining an accurate assessment of the baseline tumor status. Specifically, baseline evaluation of tumor dimensions within 28 days (for measurable disease) or 42 days (for non-measurable disease) are the current standards for Southwest Oncology Group studies and should remain as is. It should be recognized that diseases with a tendency for rapid growth or dissemination may require more stringent time frames.
- 5.5 More liberal criteria are needed to allow patients with a prior diagnosis of another malignancy to be enrolled on Southwest Oncology Group trials. Specifically, the five year disease-free criterion from other malignancies (outside of superficial squamous cell carcinoma of the skin or cervix) is unnecessary for patients with Stage IV disease in whom the median survival is usually less than one year. For studies involving such patients, a standard criterion has been created that will allow patients to have had certain prior malignancies at any time point in the past so long as they are currently without evidence of disease from that malignancy and are off all treatment for that malignancy.
- 5.6 In order to reduce the need for repetition of expensive imaging studies, the Southwest Oncology Group will limit the requirement for scans performed to confirm objective responses to Phase II trials of Investigational New Drugs (INDs) in which objective response rate is the primary endpoint. This means that in other studies (e.g., Phase II trials involving commercially available drugs and Phase III trials in which survival is the primary endpoint) objective tumor responses need only be documented by imaging studies on a single occasion. This is a departure from previous standards and has been discussed thoroughly within the Group and agreed to by CTEP.

- 5.7 We no longer have separate eligibility checklists attached to the front of protocols. We have phased out the lengthy dialogue that occurs between the individual registering the patient and the Statistical Center and we have replaced this by short series of questions designed to capture essential demographic information and a simple “yes/no” question to determine whether the patient has met the eligibility requirements of the trial.

Section 5.0 of new protocols has been changed slightly to assist the Clinical Research Associate (CRA) in identifying all data that is required to determine patient eligibility for the clinical trial.

- 5.8 Wherever possible, we have moved baseline laboratory values that have previously been required for eligibility from Section 5.0 to Section 7.0 and placed them under the new heading “Good Medical Practices”. This allows physicians to use clinical judgment to determine whether a slight laboratory abnormality is clinically significant and would put the patient at undue risk from treatment on the protocol. For example, this would allow a physician to enroll a patient with an absolute granulocyte count of 1490 onto a protocol that recommends AGCs greater than 1500. This was not permissible when these requirements were included in Section 5.0 of the protocol.

The eligibility criteria must be verified by the Study Coordinator. These define:

- 5.9 Patient population: allowable disease sites, cell types, stage, and any other appropriate disease descriptors. Any exclusions should be stated. Since the statement *histologically confirmed advanced disease* is ambiguous, provide specific histologic confirmation instructions:

- \* a biopsy of the metastatic site or recurrence is required, or
- \* prior histologic confirmation of the malignancy is required and there must be clinical evidence of recurrent or metastatic disease.

- 5.10 Acceptable disease status: measurable only, or measurable and non-measurable.

- 5.11 Prior therapy: Any previous therapies that would exclude patients should be given. Clarify if these exclusions pertain to previous therapy for the current cancer only, or for any prior or concurrent disease. Those agent(s) or modes of therapy which are either required, or allowable for eligibility should be defined.

- a. When appropriate, do not include a minimum time period since prior therapy; rather, rely on the other eligibility criteria to assure that an appropriate time period has passed for resolution of toxicities of prior treatment.
- b. If eligibility requirements do include a minimum period of time *off treatment*, specify the time period in days rather than months or weeks to ensure compliance.

- 5.12 Performance status.

- 5.13 Multiple registrations: Include a separate section to define eligibility requirements for re-registrations (e.g., at crossover). *Do not refer the reader back to the initial registration eligibility criteria section.*

- 5.14 Concurrent treatment: Eligibility Criteria may state that no concurrent treatment (chemotherapy or biologics) may be **planned** during protocol treatment; however, the general discussion of concurrent treatment should be in the treatment plan rather than eligibility. Eligibility Criteria are intended merely to determine eligibility at a fixed point in time, and may not proscribe something that may happen in the future.

- 5.15 The following is standard wording which should be included in this section if appropriate:

*Pregnant or nursing women may not participate. Women or men of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.*

*No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.*

- 5.16 Time constraints for the performance of tests are standardized by each committee and will be inserted at the Operations Office.

- 5.17 The following is standard wording which must be included in every protocol:

*All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.*

*At the time of patient registration, the treating institution's name and ID number must be provided to the Statistical Center in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.*

The Statistical Center will create a registration form which is attached to the protocol at the time of Activation.

All information required at the time of registration will be listed on the registration form (even though some of these items are not strictly applicable to eligibility).

## 6.0 **STRATIFICATION FACTORS**

Stratification is not applicable if there is no randomization or stratification. Otherwise, the stratification factors should be identified. This section must appear in all protocols.

Stratification factors are pretreatment patient characteristics which will be balanced across treatment arms. Stratification factors should be limited to two or three of the most important variables.

## 7.0 **TREATMENT PLAN**

The entire treatment or treatments should be outlined. For those studies which will include randomization, the separate regimens should be labeled with suitable abbreviations consistent with the rest of the protocol. It should be stated if the patients will be restaged and if a second registration will be required at that time. Indicate when any other registrations/randomizations should occur, such as for start of radiation therapy. Make sure this is consistent with the registration guidelines. **Do not include disease assessment information in this section; it belongs in the Study Calendar.**

The first part of Section 7.0 in most protocols will include "Good Medical Practices" defining general parameters for tests which are not required as part of the eligibility determination.

When different modes of therapy are being utilized, such as surgery or radiation therapy, each should be given in one complete section of the treatment plan. Radiation therapy guidelines have been formulated, and all protocols must have the standard format before approval will be given for NCI review. For the more complex protocols (Phase III) which contain two or more treatment modalities, the different modalities should be divided and included under separate headings, such as:

- 7.1 Treatment Plan - Surgery
- 7.2 Treatment Plan - Radiation Therapy
- 7.3 Treatment Plan - Chemotherapy

The dose(s) of drugs utilized, the schedule of the agents, and the number of courses should be clearly outlined for each treatment. Doses should always be expressed in terms of daily dose and not in terms of the cumulative dose.

The following format will be used:

AGENT	DOSE	ROUTE	RE RX DAYS	INTERVAL	NOTES
Adriamycin	50 mg/M <sup>2</sup>	IV over 5 min.	1	4 weeks	Maximum cumulative dose 500 mg/M <sup>2</sup>
Cisplatin	60 mg/M <sup>2</sup>	IV over 2 hr in 1000 ml 1/2 normal saline + 25 gm Mannitol	1	4 weeks	Give Adriamycin before Cisplatin
Pred- nisone	30 mg	PO	1-7	4 weeks	

- 7.4 Criteria for removal from protocol treatment are to be outlined. Examples of standard criteria follow. Make sure that the treatment program for all patient subgroups has a clearly defined stopping point, or if treatment is to continue indefinitely, that this is stated. This section should be consistent with any off treatment criteria outlined in the dose modification section.

**Criteria for Removal from Protocol Treatment**

- a. *After eight weeks of treatment (two courses), patients with progressive disease will be taken off treatment. Patients with complete or partial responses or stable disease will continue treatment.*
  - b. *Progression of disease (as defined in Section 10.\_\_\_\_).*
  - c. *Unacceptable toxicity.*
  - d. *The patient may withdraw from the study at any time for any reason.*
- 7.5 *All reasons for discontinuation of treatment must be documented in the Study Forms.*
  - 7.6 *All patients will be followed for five years or until death, whichever occurs first.*

## 8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE), will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located at the CTEP website at

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTEP Active Version of the CTCAE.

8.1 Chemotherapy (or hormonal, biologics) toxicities to be monitored.

List major expected toxicities (long term and short term).

8.2 Radiation toxicities (if applicable).

List major expected toxicities (long term and short term).

8.3 Surgery toxicities (if applicable).

List major expected toxicities (long term and short term).

8.4 If a toxicity is not included in the CTCAE Active Version, grades must be developed, reviewed and approved by the Operations Office and the Statistical Center. If a standard definition exists, other definitions of the toxicity may not be used. Instructions for dose modification should be inclusive of all possible toxicities and, whenever possible, should be based on the numeric toxicity grades of the CTCAE Active Version.

8.5 Dose changes (increases and decreases) should be presented in levels to minimize confusion. Providing a precise amount of drug to be administered for a defined condition reduces error and promotes consistent treatment. Indicate whether dose modifications are based on toxicity on the day of treatment or worst toxicity during the previous treatment. See tables below.

Dose Adjustments based on Day of Treatment Counts:

Granulocyte		Platelet	5-FU
≥ 1,500	and	≥ 100,000	Starting Dose
1,000 - 1,499	and	≥ 75,000	Dose Level -1
≥ 1,000	and	75,000 - 99,999	Dose Level -1
< 1,000	or	< 75,000	Hold drug one week*

\*If sufficient hematologic recovery has not occurred, (i.e., granulocytes ≥ 1,000 and platelets ≥ 75,000) after holding drug one week, hold radiation therapy in addition to the drug for an additional week. If hematologic recovery has not occurred after a total of two weeks, contact the Study Coordinator.

Dose Levels (mg/M<sup>2</sup>):

Drug	- 2	- 1	Starting Dose
5-FU	500	750	1,000

- 8.6 The following provisions for dose modification should be addressed in all protocols:
- a. Define any prestudy condition that necessitates modification of initial dose.
  - b. Define retreatment parameters (e.g., AGC  $\geq$  2,000/ $\mu$ l, platelets  $\geq$  100,000/ $\mu$ l, creatinine  $\leq$  1.5 mg%). If toxicity has not resolved at time of retreatment, define acceptable delay, dose at resumption of treatment, and what should be done if the toxicity has not resolved at the end of the delay.
  - c. If toxicity persists after one dose modification, indicate what further dose changes are required. If additional dose decreases are indicated, the dose table should accommodate multiple level decreases. If the agent is eventually permanently discontinued, or if at some point there are no further reductions, indicate this as well.
  - d. Indicate if dose increases are allowed after dose decreases. If so, to what grade of toxicity must the patient recover, what is the minimum duration of recovery prior to dose increase, how large is the dose increase and how many increases are allowed. NOTE: Tables which indicate dose levels when counts are normal should specify that dose level should be at previous dose rather than starting dose, *unless increases to starting dose after a previous decrease are actually intended*.
  - e. Indicate what dose level should be used if there are multiple toxicities. (For instance, the lowest dose indicated for any individual toxicity.)
  - f. If instructions are to use ancillary treatments, e.g., antiemetics, rather than dose reductions, indicate what measures are to be taken when the ancillary treatment is not effective.
  - g. If instructions are to delay treatment rather than reduce dosage what should be done if the toxicity has not resolved at the end of the delay, to what grade of toxicity must the patient recover, what is the minimum duration of the recovery period prior to retreatment, what dose level should be used after the delay?
  - h. Use of G-CSF must be addressed.
- 8.7 A standard statement will be added by the Operations Office to refer all treatment related questions to the Study Coordinator:

*For treatment or dose modification related questions, please contact Dr. \_\_\_\_\_ (name) \_\_\_\_\_ at \_\_\_\_\_ (telephone number) \_\_\_\_\_ or Dr. \_\_\_\_\_ (name) \_\_\_\_\_ at \_\_\_\_\_ (telephone number) \_\_\_\_\_.*

- 8.8 A standard statement will be added by the Operations Office addressing the procedure for reporting of adverse drug reactions as follows:

*Unexpected or fatal toxicities (including suspected reactions) must be reported to the Operations Office, to the Study Coordinator, to the IRB and the NCI. The procedure for reporting adverse reactions is outlined in Section 16.0.*

## 9.0 STUDY CALENDAR

A sample Study Calendar is included in chart form on page 19 of this policy. These calendars should outline every parameter/test which will be performed while the patient is on protocol treatment along with the actual therapy.

Categories to be listed are as follows (in this order): Physical; Laboratory; X-rays and Scans; and Treatment. Each test, whether it is being done prestudy only or continuously throughout the study, should be noted. It is not necessary to list every day or week throughout the life of the

study; rather, only those days in which either therapy or tests are being performed. Asterisk and footnote special instructions. All tests which will be continued after the patient stops therapy should also be indicated along with the time point at which they should be performed.

Check the Study Calendar's consistency with eligibility (all tests required for eligibility must be on the calendar), treatment plan (treatment days, tests and follow-up must match) and dose modifications (tests for toxicity monitoring must be included). A standard NOTE appears at the bottom of the calendar to refer the reader to the Master Forms Set and the Data Submission Schedule for forms submission guidelines.

**9.0 STUDY CALENDAR** √  
**S9708, Evaluation of Gemcitabine (Gemzar®) in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)**

REQUIRED STUDIES	PRE STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	Wk 19	Wk 20	Wk 21	Wk 22	Wk 23	Wk 24
PHYSICAL																	X				X				X
History and Physical Exam	X			X				X					X				X				X				X
Weight and Performance Status	X			X				X					X				X				X				X
Disease Assessment #																									
Toxicity Notation		X	X	X			X	X				X							X	X			X	X	
LABORATORY <sup>∞</sup>																									
WBC/Differential/Platelets	X	X	X	X			X	X				X							X	X			X	X	
Serum Calcium	X				X				X				X					X				X			X
Serum Creatinine	X								X				X								X				X
Calc Creatinine Clearance <sup>f</sup>	X				X				X				X								X				X
Bilirubin	X				X				X				X								X				X
SGOT or SGPT	X				X				X				X								X				X
X-RAYS AND SCANS																									
X-Rays and Scans for									X																X
Disease Assessment#	X																								
TREATMENT																									
Gemcitabine (Gemzar®)		X	X	X			X	X		X	X	X		X	X	X		X	X		X	X	X	X	X

NOTE: All forms to be utilized for this study are listed in Section 18.0. Form submission guidelines are found in Section 14.0.

- <sup>∞</sup> All labs should be done prior to each gemcitabine administration.
- <sup>f</sup> Either serum creatinine or creatinine clearance (24 hour OR calculated) may be used to document adequate renal function.
- <sup>#</sup> Measurable and evaluable disease must be assessed after two cycles (every 8 weeks) using the same techniques as for baseline assessment. Response of CR or PR must have a second confirmation at least three weeks after the first documentation of response (see Section 10.3). X-rays and scans for disease assessment should be done on Day 50 and every second cycle thereafter.
- <sup>√</sup> Gemcitabine therapy and parameters will continue at these intervals until progression of disease occurs or patient goes off protocol treatment (see Section 7.2). Once off-treatment, patients should be followed every 3 months for the first year, every 6 months for the second year, and every 12 months thereafter.

## **10.0 CRITERIA FOR EVALUATION**

There are standard endpoint criteria which will be inserted by the Operations Office. Within the endpoint criteria, disease specific references will be supplied in conjunction with the Study Coordinator and the Statistical Center. The RECIST criteria are used for solid tumor disease assessment.

## **11.0 STATISTICAL CONSIDERATIONS**

The Study Coordinator should send the concept sheet and initial draft of the protocol to the disease site statistician who will write the statistical section.

The statistical section will typically include:

- a recapitulation of study objectives
- the anticipated accrual rate, the accrual goal for the study, including accrual goals by strata if appropriate
- the study design, including contingencies for early stopping, any stratification factors, and characteristics to be incorporated in analyses
- the power of the study to address the major objective(s), the assumptions involved in the determination of power, tables of power under various alternatives
- the power of the study to address the other objective(s), the assumptions involved in the determination of power
- the criteria for study monitoring

To write this section, the Study Coordinator must discuss with the statistician the expected accrual rate, reflecting recent experience with the disease, and background information for each study objective. For noncomparative studies with the objective of ESTIMATING toxicity, response rate, survival time, response duration, time to progression, etc., the statistician will need at least an idea of the expected rate (duration) and the desired precision of the estimate. Useful information to provide would be results from other studies. If the objective is to EVALUATE an endpoint, specify what values would be of interest/not of interest to discern with the study.

## **12.0 DISCIPLINE REVIEW**

There must always be a Discipline Review section in all protocols whether it will be performed or not. If discipline review is not to be performed, the following statement should appear in Section 12.0:

*Discipline Review is not required for this study.*

The necessity for discipline review is determined by the appropriate discipline committee. Standard information for pathology review, surgery review or radiotherapy review, will be inserted by the Operations Office.

## **13.0 REGISTRATION GUIDELINES**

Certain information is standard for this section and will be supplied by the Operations Office when the protocol is formatted. This section may include information about simultaneous registration to ancillary studies.

#### 14.0 DATA SUBMISSION SCHEDULE

- 14.1 Certain information for this section is standard and will be supplied by the Operations Office when the protocol is formatted. The following statement must be included for all studies:

*Data must be submitted according to protocol requirements for ALL patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.*

- 14.2 State that master forms are included in the protocol and (with the exception of the Model Informed Consent and the Registration Form) must be photocopied for data submission to the Statistical Center.
- 14.3 The submission schedule for each form must be stated.
- 14.4 RE-REGISTRATION AND DATA SUBMISSION REQUIREMENTS: If the protocol requires re-registration, re-registration instructions must be specified. If re-registration will necessitate submission of forms, films, specimens, slides, etc., the Study Coordinator must communicate this to the Statistical Center so that appropriate instructions can be written.

#### 15.0 SPECIAL INSTRUCTIONS

Examples of items for this section include instructions to the institutional data managers/clinicians/nurses for submission of specimens (tissue for tumor cloning assay, paraffin blocks for DNA flow cytometry, tubes of blood/bone marrow for immunophenotyping by flow cytometry, peripheral blood smears/bone marrow aspirate smears for special histochemical studies), procedure for instillation of intraperitoneal drugs, etc. **DO NOT** include a description of the methods/procedures that will be used by the reference laboratory(ies); detailed methodology to be used by the reference laboratory should be circulated as an appendix to the protocol OR should be written as a separate internal protocol.

#### 16.0 ETHICAL AND REGULATORY CONSIDERATIONS

This section is standard for all Southwest Oncology Group protocols and will be provided by the Operations Office. It includes information for reporting Serious Adverse Events, and general references regarding ethical concerns.

#### 17.0 BIBLIOGRAPHY

All references must be complete. They should be numbered and listed in the order that they appear in the protocol. The general rules to be followed when listing these references are outlined below.

- 17.1 Punctuate names only by a comma between complete names; no internal punctuation.
- 17.2 Follow the names of the authors with a period before the title of the article.
- 17.3 Capitalize only the first word in the title of an article or chapter, unless there are proper names included.
- 17.4 No punctuation between the journal name and year of publication is needed.
- 17.5 Always include the page numbers of the article, volume number and year of publication.

17.6 Examples:

- a. Journal: Bodey GP, Hewlett JS, Coltman CA Jr, Rodriguez V, Freireich EJ. Adriamycin in the treatment of childhood solid tumors. *Cancer*; 36:1572-1576, 1975.
- b. Book: Freireich EJ. *Childhood Solid Tumors*. Second edition. Baltimore: Williams and Wilkins, 1972:110-147.
- c. Book Chapter: Huguley CM, Calch CM. The chronic leukemias. In: HF Conn, ed. *Current therapy*. Philadelphia: WB Saunders, 1972:286-288.
- d. Abstract: Glucksberg H, Rivkin S, Rasmussen S. Adjuvant chemotherapy for operable breast cancer with positive axillary nodes. *ASCO*: #C-367, 1981.

17.7 Double space between each complete citation.

**18.0 MASTER FORMS SET**

A complete forms set must be specified. These forms will be used as Masters for photocopying purposes by institutions.

18.1 **MODEL INFORMED CONSENT FORM:** The Study Coordinator must compose a description of the treatment and side-effects in layman's terms to be used in the consent form. The Operations Office will supply the standard sections and will also help identify the side effects of agents previously used in a protocol. All NCI ethical and regulatory guidelines must be followed in developing this form.

**19.0 APPENDIX**

This section may include other charts or special forms which are not Master forms.